IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: William J. Curatolo, et al.

SERIAL NO.: 09/742,785

FILED: December 20, 2000

FOR: Pharmaceutical Compositions Providing Enhanced Drug Concentrations

Examiner: Fubara, Blessing M.
Art Unit: 1615

Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.131

I, Douglas A. Lorenz, declare that:

1. This declaration is to establish completion of the invention of this application in the United States at a date prior to November 23, 1999, that is the effective date of U.S. Published Patent Application 2003/0215496 that was cited by the examiner, and to establish completion of the invention of this application in the United States at a date prior to February 9, 1999, that is the effective date of U.S. Patent 6,548,555 B1, also cited by the examiner.

2. I am one of the inventors of the instant application.

3. To establish the date of completion of the invention of this application, reproductions of notebook entries are submitted as evidence as Exhibit A. The actual dates in the notebook entries have been redacted.

4. From these documents it can be seen that the invention in this application was made in the United States at least by the date of February 9, 1999, which is a date earlier than the effective date of the reference.

5. In particular attached to this declaration are notebook pages related to work I supervised. These pages show that the combination of a low-solubility drug in a solubility improved form combined with a concentration-enhancing polymer results in dissolved drug concentrations that are greater than the dissolved drug concentration provided by a control composition consisting of the crystalline drug alone. In particular, pages 3-6 of Exhibit A show that the use of a high solubility salt form (namely the mesylate salt) of two different drugs physically mixed (or triturated) with the polymer hydroxypropylmethyl cellulose acetate succinate provides concentration enhancement relative to the crystalline drug alone. This work was performed prior to February 9, 1999.

DECLARATION

6. As a person signing below:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Douglas A. Lorenz

Date: 12-29-04

NOTEBOOK NO. 1442
ISSUED TO Doug Lorenz
ON redacted **19**
DEPARTMENT
RETURNED **19**

—SCIENTIFIC NOTEBOOK CO.—
2831 LAWRENCE AVE.
P.O. BOX 238
STEVENSVILLE, MI 49127
616-429-8285

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TEMPLATE FOR EXPERIMENTAL WORK

Graphs/Sketches

Estimate Trends of Key Experiment(s)

Overall Hypothesis

Physical Model of Technology or Problem

Determine the feasability of using high energy forms of CP-316,311 to increase the bioavailability and overcome a fed / fasted effect.

Specific Study Goals

What is the key question about the hypothesis these experiments will answer?

Initial spraying of dispersion for screening + initial studies

Experimental

Key Experimental Conditions

Also assay from KEC –

1:9 CP316,311 : HPMCAS-HF triturated – 1.021 mg/5 mL
20.4 ug/mL = theor, 17.4 ug/mL = actual (85%)

1:9 CP316,311 : HPMCAS-MF triturated – 1.057 mg/5 mL
21.1 ug/mL = theor 22.2 ug/mL = actual (105%)

Results/Conclusions

Key Results: Did we strengthen or weaken the hypothesis?

Initial stks were day old from CLH (perhaps evaporated slightly). Redo – looks better. See testing on later pages

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		Recorded by	

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TEMPLATE FOR EXPERIMENTAL WORK

Graphs/Sketches

Estimate Trends of Key Experiment(s)

Overall Hypothesis

Physical Model of Technology or Problem

Determine feasibility of using high energy forms of CP316,311 to increase bioavailability and overcome a bed/ fasted effect.

Specific Study Goals

What is the key question about the hypothesis these experiments will answer?

More polymer screening —

Experimental

Key Experimental Conditions

assays —

1:9 ~~CP~~ CP316,311-27 : HPMCAS-HF trit. 23.6 ug/mL theor, 22.9 ug/mL actual (97%)
2.36 mg / 10 mL

1:9 CP316,311-27 : HPMCAS-MF trit. 23.8 ug/mL theor 22.8 ug/mL actual (96%)
1.192 mg / 5 mL

Results/Conclusions

Key Results: Did we strengthen or weaken the hypothesis?

HPMC insoluble - Other sprays went OK.
Assay results look good.

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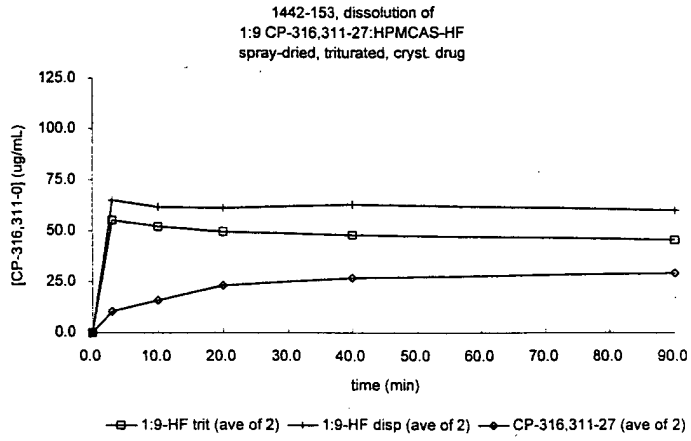
Project No.

TITLE Book No. 153

From Page No.

1442-153 – 1:9 CP-316,311-27:HPMCAS-HF – dispersion, triturated mixture, crystalline drug – Experimental conditions @ pH 6.5 –

Type of experiment:	Dissolution of CP-316,311 using centrifuge method
Drug:	2.33 mg 1:9 CP-316,311-27:HPMCAS-HF dispersion 1442-137d 2.33 mg 1:9 CP-316,311-27:HPMCAS-HF triturated 0.233 mg crushed, crystalline CP-316,311-27
Receptor solution:	1.8mL NaTC-POPC in PBS, pH 6.5, 290 mOsm/kg,
Date Performed	redacted
Operator	KEC
Notebook	1442-153
Results:	dispersion- C_{max}= 65µg/mL (FB) AUC_{90}=5,475 min*µg/mL 20h conc=58.3ug/mL triturated- C_{max}=55µg/mL (FB) AUC_{90}=4,297 min*µg/mL 20h conc=38.5ug/mL crystalline C_{max}=29µg/mL (FB) AUC_{90}=2,215 min*µg/mL 20h conc=32.2ug/mL
Comments	All work done in 37C controlled temp box. Theoretical Cmax (free base) based on the assay results is 95.5µg/mL for the dispersion, 85µg/mL for the triturated mixture, and 100µg/mL for the crystalline CP-316,311-27.



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Project No.

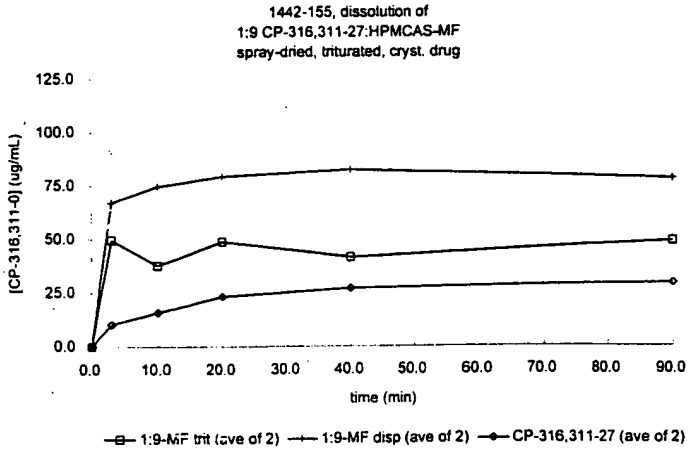
TITLE Book No. 155

From Page No.

1442-155 — 1:9 CP-316,311-27:HPMCAS-MF dispersion, triturated mixture crystalline drug. Procedure + experimental details @ bft.

using centrifuge method

Drug:	2.33 mg 1:9 CP-316,311-27:HPMCAS-MF dispersion 1442-137e 2.33 mg 1:9 CP-316,311-27:HPMCAS-MF triturated 0.233 mg crushed, crystalline CP-316,311-27
Receptor solution:	1.8mL NaTC-POPC in PBS, pH 6.5, 290 mOsm/kg.
Date Performed	redacted
Operator	KEC
Notebook	1442-155
Results:	dispersion- C_{max}= 82µg/mL (FB) AUC_{90}=6,987 min*µg/mL 20h conc=49.4ug/mL triturated- C_{max}=55µg/mL (FB) AUC_{90}=3,979 min*µg/mL 20h conc=36.8ug/mL crystalline C_{max}=29µg/mL (FB) AUC_{90}=2,215 min*µg/mL 20h conc=32.2ug/mL
Comments	All work done in 37C controlled temp box. Theoretical Cmax (free base) based on the assay results is 101µg/mL for the dispersion, 96µg/mL for the triturated mixture, and 100µg/mL for the crystalline CP-316,311-27.



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Project No._____

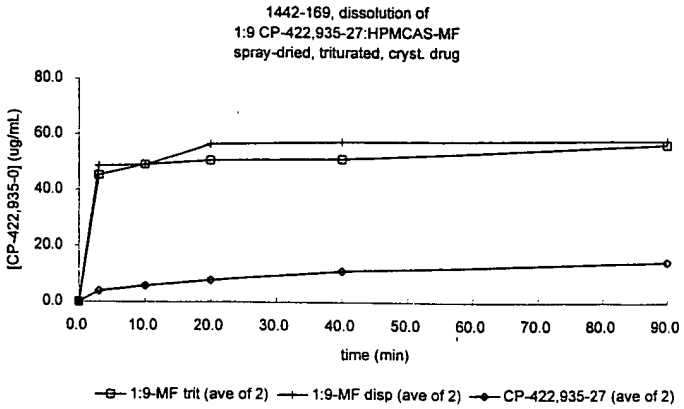
TITLE _____ Book No._____ 169

From Page No.__ 1442-169

Dissolution tests for CP-422,935-27: HPMCAS-MF (1:9) dispersion, triturated mixture, and crystalline drug.

Spray information on p. 165 —

Type of experiment:	Dissolution of CP-422,935 using centrifuge method
Drug:	1.8 mg 1:9 CP-422,935-27:HPMCAS-MF dispersion 1442-165b 1.8 mg 1:9 CP-422,935-27:HPMCAS-MF triturated 0.18 mg crushed, crystalline CP-422,935-27
Receptor solution:	1.8mL NaTC-POPC in PBS, pH 6.5, 290 mOsm/kg,
Date Performed	redacted
Operator	KEC
Notebook	1442-169
Results:	dispersion- C_{max}= 58.1µg/mL (FB) AUC_{20}=4,971 min*µg/mL 20h conc= 48.0 ug/mL triturated- C_{max}=56.7µg/mL (FB) AUC_{20}=4,622 min*µg/mL 20h conc= 33.5 ug/mL crystalline C_{max}=14.7µg/mL (FB) AUC_{20}=945 min*µg/mL 20h conc= 18.9 ug/mL
Comments	All work done in 37C controlled temp box. Theoretical Cmax (free base) based on the assay results is 63.0µg/mL for the dispersion, 66.4µg/mL for the triturated mixture, and 66.3µg/mL for the crystalline CP-422,935-27.



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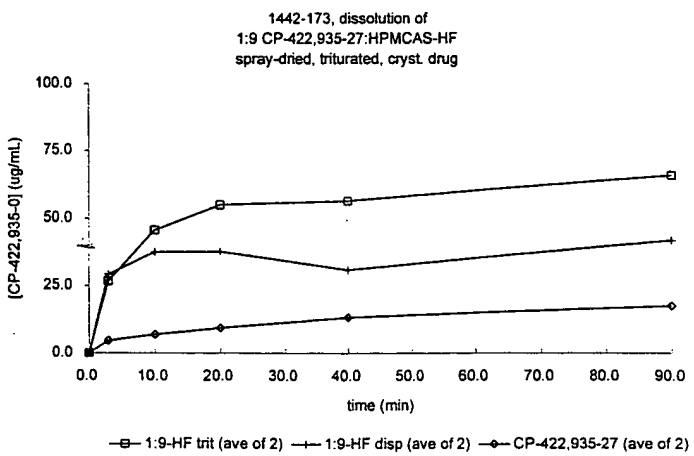
TITLE_____ Book No._____ 173

From Page No._ 1442-173

Dissolution Test – 1:9 CP-422,935-27:HPMCAS-HF Dispersion, Triturated mixture, plain xtalline drug

See spray information on p. 165 –

Type of experiment:	Dissolution of CP-422,935 using centrifuge method
Drug:	1.8 mg 1:9 CP-422,935-27:HPMCAS-HF dispersion 1442-165a 1.8 mg 1:9 CP-422,935-27:HPMCAS-HF triturated 0.18 mg crushed, crystalline CP-422,935-27
Receptor solution:	1.8mL NaTC-POPC in PBS, pH 6.5, 290 mOsm/kg,
Date Performed	redacted
Operator	KEC
Notebook	1442-173
Results:	dispersion- C_{max}= 34.8µg/mL (FB) AUC_{90}=2,662 min*µg/mL 20h conc= 43.3 ug/mL triturated- C_{max}=54.7µg/mL (FB) AUC_{90}=4,130 min*µg/mL 20h conc= 51.0 ug/mL crystalline C_{max}=14.7µg/mL (FB) AUC_{90}=945 min*µg/mL 20h conc= 18.9 ug/mL
Comments	All work done in 37C controlled temp box. Theoretical Cmax (free base) based on the assay results is 61.7µg/mL for the dispersion, 63.6µg/mL for the triturated mixture, and 66.3µg/mL for the crystalline CP-422,935-27.



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